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L1              1 SEA ABB=ON  PLU=ON  US2005-527481/AP
                  SEL RN

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L2              1 SEA ABB=ON  PLU=ON  501951-42-4/BI

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L3              1 SEA ABB=ON  PLU=ON  L1 AND L2
                  D IALL HITSTR

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L4                STR 501951-42-4
L5              0 SEA FAM SAM L4
L6              2 SEA FAM FUL L4
                  D SCA
                  D LC 1-2

     FILE 'CAPLUS, IMSRESEARCH, IMSDRUGNEWS, PROUSDDR' ENTERED AT 15:55:47 ON
     21 SEP 2006
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L8             10 DUP REM L7 (0 DUPLICATES REMOVED)
                       ANSWERS '1-5' FROM FILE CAPLUS
                       ANSWER '6' FROM FILE IMSRESEARCH
                       ANSWERS '7-9' FROM FILE IMSDRUGNEWS
                       ANSWER '10' FROM FILE PROUSDDR

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     SEP 2006
                  E DAVIS J/AU
L9           3477 SEA ABB=ON  PLU=ON  ("DAVIS J"/AU OR "DAVIS J B"/AU OR "DAVIS
                  J B JR"/AU OR "DAVIS JOHN"/AU OR "DAVIS JOHN B"/AU OR "DAVIS
                  JOHN B JR"/AU OR "DAVIS JOHN BERESFORD"/AU)
                  E WINCHESTER W/AU
L10            42 SEA ABB=ON  PLU=ON  ("WINCHESTER W"/AU OR "WINCHESTER W J"/AU
                  OR "WINCHESTER WENDY"/AU OR "WINCHESTER WENDY J"/AU OR
                  "WINCHESTER WENDY JOYCE"/AU)
L11            11 SEA ABB=ON  PLU=ON  L9 AND L10
L12          3508 SEA ABB=ON  PLU=ON  (L9 OR L10)
L13           195 SEA ABB=ON  PLU=ON  L12 AND ?VANILL?
L14             9 SEA ABB=ON  PLU=ON  L13 AND (RECEP?(5A) ANTAG? AND PAIN)
L15            18 SEA ABB=ON  PLU=ON  L11 OR L14
L16            12 DUP REM L15 (6 DUPLICATES REMOVED)
                       ANSWERS '1-5' FROM FILE HCAPLUS
                       ANSWER '6' FROM FILE MEDLINE
                       ANSWERS '7-8' FROM FILE EMBASE
                       ANSWERS '9-12' FROM FILE BIOSIS

=> fil hcap
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 21 Sep 2006 VOL 145 ISS 13
FILE LAST UPDATED: 20 Sep 2006 (20060920/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que l3
L1 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US2005-527481/AP
L2 1 SEA FILE=REGISTRY ABB=ON PLU=ON 501951-42-4/BI
L3 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 AND L2

INSTANT APPLICATION

=> d l3 iall hitstr

L3 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:252345 HCAPLUS Full-text
DOCUMENT NUMBER: 140:264523
ENTRY DATE: Entered STN: 26 Mar 2004
TITLE: Use of vanilloid receptor antagonists for the treatment of pain
INVENTOR(S): Davis, John Beresford; Winchester, Wendy Joyce
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-4439
SECONDARY: A61K045-00; A61P001-00; A61P013-00; A61P029-00
CLASSIFICATION: 1-11 (Pharmacology)
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024154	A1	20040325	WO 2003-EP10261	20030910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2003264297	A1	20040430	AU 2003-264297	20030910

EP 1545522	A1	20050629	EP 2003-795018		20030910
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JP 2006502173	T2	20060119	JP 2004-535516		20030910
US 2005239846	A1	20051027	US 2005-527481		20050311 <--
PRIORITY APPLN. INFO.:			GB 2002-21157	A	20020912
			WO 2003-EP10261	W	20030910

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004024154	ICM	A61K031-4439
	ICS	A61K045-00; A61P001-00; A61P013-00; A61P029-00
	IPCI	A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0045-00 [ICS,7]; A61P0001-00 [ICS,7]; A61P0013-00 [ICS,7]; A61P0029-00 [ICS,7]
	IPCR	A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]
	ECLA	A61K031/4439
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EP 1545522	IPCI	A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0045-00 [ICS,7]; A61P0001-00 [ICS,7]; A61P0013-00 [ICS,7]; A61P0029-00 [ICS,7]
	IPCR	A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]
	ECLA	A61K031/4439
JP 2006502173	IPCI	A61K0045-00 [I,A]; A61K0031-4439 [I,A]; A61K0031-4427 [I,C*]; A61P0029-00 [I,A]; A61P0043-00 [I,A]; C07D0401-04 [I,A]; C07D0401-00 [I,C*]
	FTERM	4C063/AA01; 4C063/BB02; 4C063/CC12; 4C063/DD03; 4C063/EE01; 4C084/AA17; 4C084/NA14; 4C084/ZA082; 4C084/ZC022; 4C086/AA01; 4C086/BC17; 4C086/GA07; 4C086/GA08; 4C086/MA01; 4C086/MA04; 4C086/NA14; 4C086/ZA08; 4C086/ZC02
US 2005239846	IPCI	A61K0031-4745 [ICM,7]; A61K0031-4738 [ICM,7,C*]; A61K0035-78 [ICS,7]
	IPCR	A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]
	NCL	514/343.000; 424/760.000
	ECLA	A61K031/4439

ABSTRACT:
The invention discloses a method for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia, and pain associated therewith, in humans or non-human mammals, which comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a vanilloid receptor antagonist.

SUPPL. TERM: vanilloid receptor antagonist pain treatment

INDEX TERM: Disease, animal
(Barrett's metaplasia; vanilloid receptor antagonists for treatment of pain)

INDEX TERM: Cation channel
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(TRPV1 (transient receptor potential cation channel subfamily V member 1); vanilloid receptor antagonists for treatment of pain)

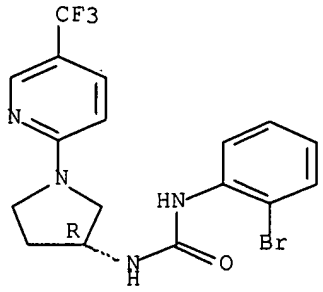
INDEX TERM: Biliary tract, disease
(biliary colic; vanilloid receptor antagonists for treatment of pain)

INDEX TERM: Disease, animal

(dysphagia; vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Dyspepsia
(functional; vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Body, anatomical
(pelvis, pelvic pain; vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Digestive tract, disease
(pyrosis; vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Kidney, disease
(renal colic; vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Capsaicin receptors
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(type VR1; vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Analgesics
Drug delivery systems
Gastrointestinal agents
Human
Pain
(vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Capsaicin receptors
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(vanilloid receptor antagonists for treatment of pain)
INDEX TERM: Drugs
(veterinary; vanilloid receptor antagonists for treatment of pain)
INDEX TERM: **501951-42-4**
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vanilloid receptor antagonists for treatment of pain)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD.
REFERENCE(S):
(1) Adrian, W; WO 02072536 A 2002 HCAPLUS
(2) Bakthavatchalam, R; WO 0208221 A 2002 HCAPLUS
(3) Bortolotti, M; ALIMENTARY PHARMACOLOGY AND THERAPEUTICS 2002, V16(6), P1075 MEDLINE
(4) Hee Doo, K; WO 0216317 A 2002 HCAPLUS
(5) Jason, M; WO 03068749 A 2003 HCAPLUS
(6) Kantilal, R; WO 02090326 A 2002 HCAPLUS
(7) Kantilal, R; WO 03022809 A 2003 HCAPLUS
(8) Kantilal, R; WO 03053945 A 2003 HCAPLUS
(9) Lazzeri, M; JOURNAL OF UROLOGY 1996, V156(3), P947 HCAPLUS
(10) William, D; WO 9963986 A 1999 HCAPLUS

IT **501951-42-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vanilloid receptor antagonists for treatment of pain)
RN 501951-42-4 HCAPLUS
CN Urea, N-(2-bromophenyl)-N'-[(3R)-1-[5-(trifluoromethyl)-2-pyridinyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


CF3
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PRIOR ART SEARCH

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Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
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ENTER A FILE NAME OR (IGNORE):end

=> fil caplus imsresearch imsdrugnews prousddr
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L4                STR
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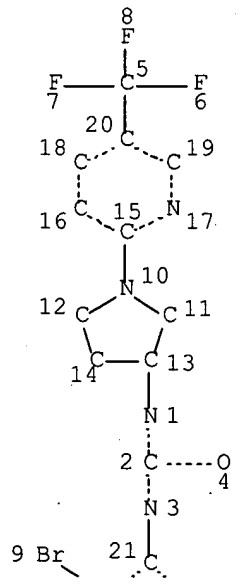

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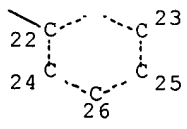

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Page 2-A
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  26

STEREO ATTRIBUTES: NONE
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L7            10 SEA L6


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DUPLICATE IS NOT AVAILABLE IN 'IMSRESEARCH, PROUSDDR'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
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                 ANSWER '6' FROM FILE IMSRESEARCH
                 ANSWERS '7-9' FROM FILE IMSDRUGNEWS
                 ANSWER '10' FROM FILE PROUSDDR

=> d l17 ibib abs hitstr 1-5

L17  ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:453918  CAPLUS  Full-text
DOCUMENT NUMBER:          145:76019
TITLE:                    Discovery of SB-705498: A potent, selective and orally
                          bioavailable TRPV1 antagonist suitable for clinical
                          development
AUTHOR(S):                Rami, Harshad K.; Thompson, Mervyn; Stemp, Geoffrey;
                          Fell, Steve; Jerman, Jeffrey C.; Stevens, Alexander
                          J.; Smart, Darren; Sargent, Becky; Sanderson, Dominic;
                          Randall, Andrew D.; Gunthorpe, Martin J.; Davis, John
                          B.
CORPORATE SOURCE:         Neurology and GI CEDD, GlaxoSmithKline, Essex, CM19
                          5AW, UK
SOURCE:                   Bioorganic & Medicinal Chemistry Letters (2006),
                          16(12), 3287-3291
                          CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:                Elsevier B.V.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
GI
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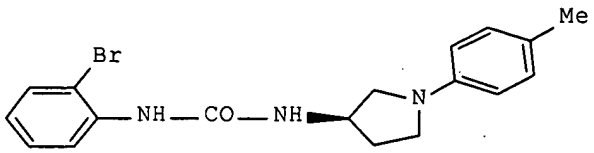

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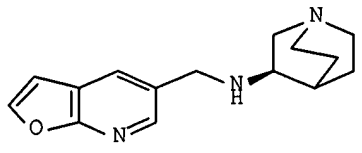


II

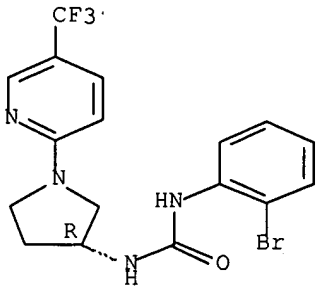
AB Small mol. antagonists of the vanilloid receptor TRPV1 (also known as VR1) are disclosed. Pyrrolidinyl ureas such as (I) and (II) (SB-705498) emerged as lead compds. following optimization of the previously described urea SB-452533. Pharmacol. studies using electrophysiol. and FLIPR-Ca2+-based assays showed that compds. such as I and II were potent antagonists vs. the multiple chemical and phys. modes of TRPV1 activation (namely capsaicin, acid and noxious heat). Furthermore, II possessed suitable lead compound properties to enable progression of this compound into in vivo studies and subsequently clin. development.

IT **501951-42-4P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(SB-705498, a potent, selective and orally bioavailable TRPV1 antagonist suitable for clin. development)

RN 501951-42-4 CAPLUS

CN Urea, N-(2-bromophenyl)-N'-[(3R)-1-[5-(trifluoromethyl)-2-pyridinyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:961880 CAPLUS Full-text
DOCUMENT NUMBER: 143:242009
TITLE: Novel therapy for renal disorders with vanilloid receptor antagonists

INVENTOR(S): Kikkawa, Hideo; Kinoshita, Mine; Mizukami, Akiko; Ozawa, Kazunori
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005079192	A2	20050901	WO 2004-US30272	20040915
WO 2005079192	A3	20051124		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

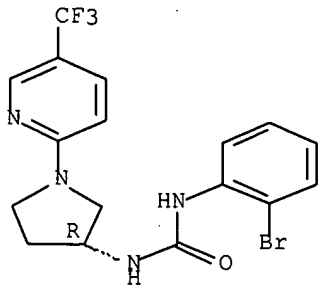
PRIORITY APPLN. INFO.: US 2003-506209P P 20030926

AB This invention relates to a novel treatment and in particular to a method for the treatment and/or prophylaxis of renal dysfunction (or disorders) associated with diseases, such as, diabetic nephropathy, glomerular nephritis, nephrosis, congestive heart failure, as well as renal dysfunctions (.apprx.r disorders) induced by drugs, including, but not limited, to antineoplastic agents, antibiotics, and immunosuppressants.

IT **501951-42-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapy for renal disorders with vanilloid receptor antagonists)

RN 501951-42-4 CAPLUS
CN Urea, N-(2-bromophenyl)-N'-[(3R)-1-[5-(trifluoromethyl)-2-pyridinyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:550885 CAPLUS Full-text

DOCUMENT NUMBER: 141:99723
TITLE: Combinations of a vanilloid antagonist and an NSAID for the treatment of pain
INVENTOR(S): Bountra, Charanjit; Davis, John Beresford; Rami, Harshad Kantilal; Thompson, Mervyn
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004056394	A1	20040708	WO 2003-EP14776	20031217
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EP 1572237	A1	20050914	EP 2003-785923	20031217
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JP 2006512345	T2	20060413	JP 2004-561422	20031217
US 2006093687	A1	20060504	US 2005-540100	20050620

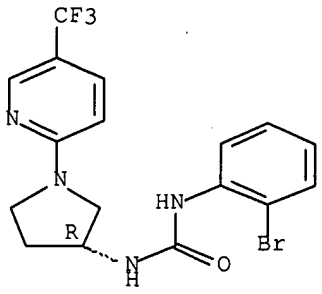
PRIORITY APPLN. INFO.: GB 2002-29808 A 20021220
WO 2003-EP14776 W 20031217

AB A method of treating conditions associated with pain and alleviating the symptoms associated therewith comprises administering to a mammal, including man, a vanilloid VR-1 antagonist or a pharmaceutically acceptable derivative thereof and an NSAID or a pharmaceutically acceptable derivative thereof, wherein said VR-1 antagonist or said NSAID may optionally be administered as a sub-maximal amount For example, a VR-1 antagonist, N-(2-bromophenyl)-N'-[((R)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3- yl)]urea (I) (preparation given), at oral dose 1 mg/kg and rofecoxib at oral dose of 1.5 mg/kg reversed a FCA-induced mech. hypersensitivity in guinea pigs by 32.5% and 30.6%, resp. However, combination of I and rofecoxib reversed the mech. hypersensitivity by 51.8%.

IT **501951-42-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combinations of vanilloid antagonist and NSAID for treatment of pain)

RN 501951-42-4 CAPLUS
CN Urea, N-(2-bromophenyl)-N'-[(3R)-1-[5-(trifluoromethyl)-2-pyridinyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:252345 CAPLUS Full-text
DOCUMENT NUMBER: 140:264523
TITLE: Use of vanilloid receptor antagonists for the treatment of pain
INVENTOR(S): Davis, John Beresford; Winchester, Wendy Joyce
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

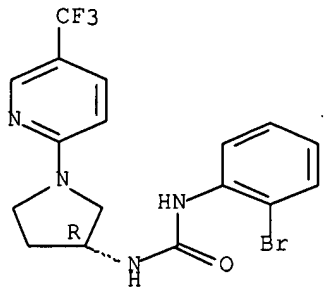
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024154	A1	20040325	WO 2003-EP10261	20030910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003264297	A1	20040430	AU 2003-264297	20030910
EP 1545522	A1	20050629	EP 2003-795018	20030910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006502173	T2	20060119	JP 2004-535516	20030910
US 2005239846	A1	20051027	US 2005-527481	20050311
PRIORITY APPLN. INFO.:			GB 2002-21157 A	20020912
			WO 2003-EP10261 W	20030910

AB The invention discloses a method for the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia, and pain associated therewith, in humans or non-human mammals, which comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a vanilloid receptor antagonist.

IT **501951-42-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(vanilloid receptor antagonists for treatment of pain)
RN 501951-42-4 CAPLUS
CN Urea, N-(2-bromophenyl)-N'-[(3R)-1-[5-(trifluoromethyl)-2-pyridinyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:221654 CAPLUS Full-text
DOCUMENT NUMBER: 138:238029
TITLE: Preparation of ureas as vanilloid receptor (VR1) antagonists
INVENTOR(S): Rami, Harshad Kantilal; Thompson, Mervyn; Wyman, Paul Adrian
PATENT ASSIGNEE(S): Smithkline Beecham P.L.C., UK
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022809	A2	20030320	WO 2002-GB4206	20020913
WO 2003022809	A3	20030717		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2458632	AA	20030320	CA 2002-2458632	20020913
EP 1425277	A2	20040609	EP 2002-765023	20020913
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BR 2002012468	A	20041019	BR 2002-12468	20020913

CN 1553905	A	20041208	CN 2002-817717		20020913
JP 2005504074	T2	20050210	JP 2003-526885		20020913
ZA 2004001186	A	20041029	ZA 2004-1186		20040213
NO 2004001003	A	20040604	NO 2004-1003		20040310
PRIORITY APPLN. INFO.:			GB 2001-22156	A	20010913
			GB 2001-30503	A	20011220
			GB 2001-30505	A	20011220
			GB 2001-30547	A	20011220
			WO 2002-GB4206	W	20020913

OTHER SOURCE(S): MARPAT 138:238029

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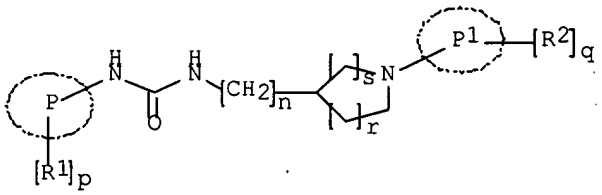

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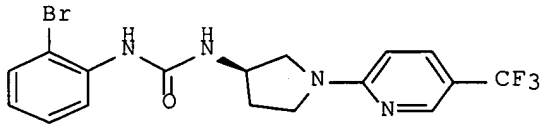


II

AB The title compds. [I; P, P1 = (hetero)aryl; R1, R2 = H, halo, alkyl, etc.; n = 0-3; p, q = 0-4; r = 1-3; s = 0-2], useful in medicine for the treatment and/or prophylaxis of pain, were prepared Thus, reacting 2-bromophenyl isocyanate with (R)-1-(5-trifluoromethylpyridin-2-yl)- pyrrolidin-3-ylamine [claimed to be prepared starting from 2-chloro-5-trifluoromethylpyridine and (3R)-3-(tert- butoxycarbonylamino)pyrrolidine; no data given] afforded (3R)-II. All compds., tested for vanilloid receptor (VR1) antagonist activity, had pKb > 6, preferred compds. having a pKb > 7.0.

IT **501951-42-4P 501952-14-3P**

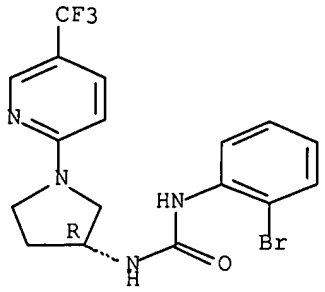
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of ureas as vanilloid receptor (VR1) antagonists for treating pain)

RN 501951-42-4 CAPLUS

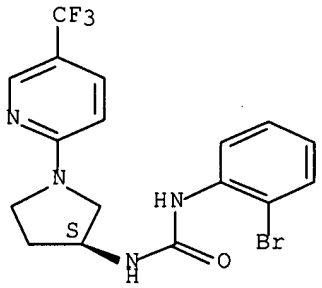
CN Urea, N-(2-bromophenyl)-N'-[(3R)-1-[5-(trifluoromethyl)-2-pyridinyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 501952-14-3 CAPLUS
CN Urea, N-(2-bromophenyl)-N'-[(3S)-1-[5-(trifluoromethyl)-2-pyridinyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

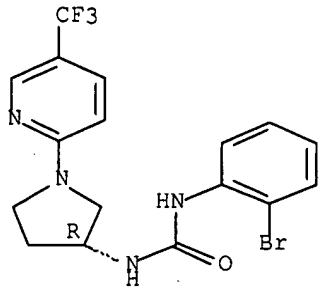


⇨ d l17 all 6-10

L17 ANSWER 6 OF 10 IMSRESEARCH COPYRIGHT 2006 IMSWORLD on STN

AN 2005:445 IMSRESEARCH
SO R&D Focus, (23 Jan 2006)
CN 705498
CN 1-(2-bromophenyl)-3-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-yl]urea
RN **501951-42-4**
STR

Absolute stereochemistry.



RN Derivatives: **501952-14-3S-isomer**
CC N2C9 All Other Antimigraine Preparations; N2B Non-Narcotic Analgesics
CT Indication: migraine; pain
Pharmacology: analgesic; vanilloid receptor antagonist
HDP Phase II (40)
LI UPDATE: Analyst prediction. ....GlaxoSmithKline reported on 30 November 2005 that phase II trials of 705498 are under way in Europe, for the treatment of acute migraine. The agent is a vanilloid receptor 1 (VR 1) antagonist.

DSTA

Type	Status	Stage	Region	Indication
Highest Phase	Phase II	40		
Phase	Phase II		Europe	migraine

CO

Type	Company	Nationality
Originator	GlaxoSmithKline	United Kingdom
Assignee	SmithKline Beecham	

TX Patent Summary: Product: WO 03/22809 2003, priority GB 22156 2001, designating 116 states.
Commercial Summary: GlaxoSmithKline is developing 705498, a vanilloid receptor 1 (VR 1) antagonist, for the potential treatment of acute migraine. 705498 may also have potential in the treatment of neuropathic pain. Phase II trials are being conducted in Europe for the treatment of acute migraine. In September 2001, SmithKline Beecham (now GlaxoSmithKline) filed a priority product patent application in the UK. GlaxoSmithKline is conducting phase II trials of 705498, in Europe, for the treatment of acute migraine (GlaxoSmithKline, NOV 2005). Phase I trials of 705498 were under way in the UK (GlaxoSmithKline, MAR 2005). Results from preclinical studies, demonstrating the potential of 705498 in the treatment of neuropathic pain, have been reported (GlaxoSmithKline, AUG 2005). Morgan Stanley Analyst, Morgan Stanley, reporting on GlaxoSmithKline, estimates sales for 705498 of US$23 million in 2009, US$68 million in 2010 and US$136 million in 2011 and estimates risk adjusted peak sales of US$226 million (Morgan Stanley, DEC 2005).
Scientific Summary: In preclinical studies, 705498 had an IC50 of less than 10 mcM. The compound inhibited capsaicin and acid-mediated

activation of hTRPV1 and inhibited heat-mediated activation of hTRPV1. 705498 inhibited hyperalgesia in the FCA (Freund's complete adjuvant) guinea pig model of pain, with an ED50 of 2.0 mg/kg po. 705498 had good oral bioavailability and pharmacokinetics, and a solubility of 0.4 mg/mL in simulated gastric fluid (GlaxoSmithKline, AUG 2005).

RDAT: 2H 2005 RNTE: Phase II, Europe (acute migraine).
2004 Phase I, UK.
SEP 2001 Priority product patent application filed in the UK, by SmithKline Beecham.

L17 ANSWER 7 OF 10 IMSDRUGNEWS COPYRIGHT 2006 IMSWORLD on STN

AN 2005:7552 IMSDRUGNEWS
TI 705498 GlaxoSmithKline phase change II, Europe (migraine)
SO R&D Focus Drug News (19 Dec 2005).
WC 33
TX GlaxoSmithKline reported on 30 November 2005 that phase II trials of 705498 are under way in Europe, for the treatment of acute migraine. The agent is a vanilloid receptor 1 (VR 1) antagonist.

CN 705498
RN **501951-42-4**
CC N2C9 All Other Antimigraine Preparations; N2B Non-Narcotic Analgesics
CO GlaxoSmithKline
DSTA Phase II. Europe
STA new phase

L17 ANSWER 8 OF 10 IMSDRUGNEWS COPYRIGHT 2006 IMSWORLD on STN

AN 2005:5752 IMSDRUGNEWS
TI 705498 GlaxoSmithKline preclinical data
SO R&D Focus Drug News (19 Sep 2005).
WC 130
TX At the 230th American Chemical Society national meeting, 28 August-1 September 2005, Washington, DC, USA, GlaxoSmithKline reported results from preclinical studies of 705498. In preclinical studies, 705498 had an IC50 of less than 10 mcM. The compound inhibited capsaicin and acid-mediated activation of hTRPV1 and inhibited heat-mediated activation of hTRPV1. 705498 inhibited hyperalgesia in the FCA (Freund's complete adjuvant) guinea pig model of pain, with an ED50 of 2.0 mg/kg po. 705498 had good oral bioavailability and pharmacokinetics, and a solubility of 0.4 mg/mL in simulated gastric fluid.

705498, a vanilloid receptor (VR 1) antagonist, is being developed for the potential treatment of pain. GlaxoSmithKline is conducting phase I trials to evaluate the agent in the treatment of migraine. The agent may also have potential in the treatment of neuropathic pain.

CN 705498
RN **501951-42-4**
CC N2C9 All Other Antimigraine Preparations; N2B Non-Narcotic Analgesics
CO GlaxoSmithKline
DSTA preclinical data.

L17 ANSWER 9 OF 10 IMSDRUGNEWS COPYRIGHT 2006 IMSWORLD on STN

AN 2005:1884 IMSDRUGNEWS

TI 705498 GlaxoSmithKline phase change I, UK
SO R&D Focus Drug News (28 Mar 2005).
WC 34
TX During March 2005 GlaxoSmithKline reported that phase I trials are under way in the UK with 705498, a vanilloid receptor 1 (VR 1) antagonist. The agent has potential for the treatment of acute migraine.

CN 705498
RN **501951-42-4**
CC N2C9 All Other Antimigraine Preparations; N2B Non-Narcotic Analgesics
CO GlaxoSmithKline
DSTA Phase I. United Kingdom
STA new drug; new phase

L17 ANSWER 10 OF 10 PROUSDDR COPYRIGHT 2006 PROUS SCIENCE on STN
AN 2006:9 PROUSDDR Full-text
DN 385281
CN N-(2-Bromophenyl)-N'-(1-(5-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3(R)-yl)urea
CN DRUG NAME: 705498
SB-705498
RN **501951-42-4**
501952-14-3 (enantiomer)
MF C17 H16 Br F3 N4 O
STA Actively Investigated
HDP PHASE II
CO ORIGINATOR: GlaxoSmithKline
CC Non-Opioid Analgesics; Acute Attacks of Migraine, Treatment of
ED Entered STN: 3 Jan 2006
Last Updated on STN: 1 Sep 2006

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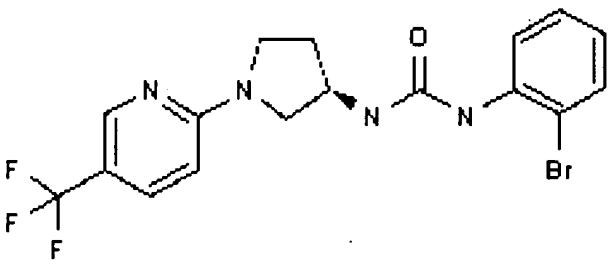

PROUS REFERENCES:

RE RefID: 944356 (Text Available)
Drug Data Report, Vol. 27, No. 10, pp 894, 2005

RTX RefID: 944356
ACTION- Potent and selective transient receptor potential vanilloid type 1 receptor (TRPV1) antagonist that antagonized human, rat and guinea pig TRPV1 orthologues with pKb values of 7.6, 7.5, 7.3, respectively, in a Ca2+-based FLIPR assay. In whole cell patch clamp electrophysiology studies, compound caused rapid and reversible inhibition of capsaicin (IC50 = 3 nM)-, acid- and heat (IC50 = 6 nM)-mediated activation of human TRPV1; it displayed voltage-dependence, suggesting an enhancement of

inhibition at negative potentials. This compound demonstrated improved solubility and oral bioavailability compared to SB-452533 (TRPV1 antagonist) and possessed favorable clearance rates, half-lives and oral bioavailabilities in both rats and dogs. It reduced capsaicin-evoked secondary hyperalgesia, reversed mechanical allodynia in the Freund's complete adjuvant inflammatory hyperalgesia model (ED50 = 2.1 mg/kg) and prevented thermal hyperalgesia in a model of neuropathic pain. Onset of analgesia was rapid, with maximal reversal achieved at 30 min post dose. Compound is currently in phase I study for migraine.

PATENT REFERENCES:

TI Use of vanilloid receptor antagonists for the treatment of pain
IN Davis, J.B.; Winchester, W.J.
PA GlaxoSmithKline
PI JP 2006502173 20060119
WO 2004024154 20040325
PRAI GB 2002-21157 20020912

TI Novel compounds
IN Thompson, M.; Wyman, P.A.; Rami, H.K.
PA GlaxoSmithKline
PI EP 1425277 20040609
JP 2005504074 20050210
WO 2003022809 20030320
PRAI GB 2001-22156 20010913
GB 2001-30503 20011220
GB 2001-30505 20011220
GB 2001-30547 20011220

TI Combinations of a vanilloid antagonist and an NSAID for the treatment of pain
IN Thompson, M.; Rami, H.K.; Bountra, C.; Davis, J.B.
PA GlaxoSmithKline
PI WO 2004056394 20040708
PRAI GB 2002-29808 20021220

REFERENCES:

RE (1) RefID: 854650, Company Communication
"Product development pipeline"
GlaxoSmithKline Product Pipeline, (November), 2004

(2) RefID: 938969, Congress Literature
"SB-705498: A novel potent and selective TRPV1 antagonist, which inhibits the capsaicin-, acid-, and heat-mediated activation of the receptor"
Gunthorpe, M.J.; et al., Annu Meet Soc Neurosci (35th Edition), Nov 12 2005-Nov 16 2005, Washington DC, (Abst 36.7)

(3) RefID: 939819, Congress Literature
"SB-705498, a clinical candidate with antagonist activity at TRPV1 and efficacy in a wide range of preclinical pain models"
Davis, J.B.; et al., Annu Meet Soc Neurosci (35th Edition), Nov 12 2005-Nov 16 2005, Washington DC, (Abst 364.2)

(4) RefID: 963670, Company Communication
"SB-705498 dental pain study (NCT00281684)"
ClinicalTrials.gov Web Site, January 28, 2006

(5) RefID: 985616, Congress Literature
"The TRPV1 antagonist SB705498 attenuates TRPV1 receptor-mediated activity and inhibits inflammatory hyperalgesia in humans: Results from a phase 1 study"
Chizh, B.; Napolitano, A.; O'Donnell, M.; et al., Annu Sci Meet Am Pain Soc (25th Edition), May 3 2006-May 6 2006, San Antonio, (Abst 765)

(6) RefID: 996732, Periodic Publication
"Discovery of SB-705498: A potent, selective and orally bioavailable TRPV1 antagonist suitable for clinical development"
Rami, H.K.; Thompson, M.; Stemp, G.; Fell, S.; Jerman, J.C.; Stevens, A.J.; Smart, D.; Sargent, B.; Sanderson, D.; Randall, A.D.; Gunthorpe, M.J.; Davis, J.B., Bioorg Med Chem Lett, Vol. 16, No. 12, pp 3287, 2006

INVENTOR SEARCH

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=> d que l16
L9         3477 SEA ("DAVIS J"/AU OR "DAVIS J B"/AU OR "DAVIS J B JR"/AU OR
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                OR "DAVIS JOHN BERESFORD"/AU)
L10          42 SEA ("WINCHESTER W"/AU OR "WINCHESTER W J"/AU OR "WINCHESTER
                WENDY"/AU OR "WINCHESTER WENDY J"/AU OR "WINCHESTER WENDY
                JOYCE"/AU)
L11          11 SEA L9 AND L10
L12        3508 SEA (L9 OR L10)
L13         195 SEA L12 AND ?VANILL?
L14           9 SEA L13 AND (RECEP?(5A) ANTAG? AND PAIN)
L15          18 SEA L11 OR L14
L16          12 DUP REM L15 (6 DUPLICATES REMOVED)

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(Y)/N:y


L16  ANSWER 1 OF 12  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER:        2004:252345  HCAPLUS  Full-text
DOCUMENT NUMBER:         140:264523
TITLE:                   Use of vanilloid receptor
                         antagonists for the treatment of pain
INVENTOR(S):             Davis, John Beresford; Winchester,
                         Wendy Joyce
PATENT ASSIGNEE(S):      Glaxo Group Limited, UK
SOURCE:                  PCT Int. Appl., 17 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ----------------    ----   --------    --------------------   --------
     WO 2004024154        A1    20040325    WO 2003-EP10261        20030910
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003264297	A1	20040430	AU 2003-264297	20030910
EP 1545522	A1	20050629	EP 2003-795018	20030910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006502173	T2	20060119	JP 2004-535516	20030910
US 2005239846	A1	20051027	US 2005-527481	20050311
PRIORITY APPLN. INFO.:			GB 2002-21157 A	20020912
			WO 2003-EP10261 W	20030910

AB The invention discloses a method for the treatment and/or prophylaxis of pelvic **pain**, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia, and **pain** associated therewith, in humans or non-human mammals, which comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a **vanilloid receptor antagonist**.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3

ACCESSION NUMBER:	2004:1017000 HCAPLUS Full-text
DOCUMENT NUMBER:	142:20714
TITLE:	Jejunal afferent nerve sensitivity in wild-type and TRPV1 knockout mice
AUTHOR(S):	Rong, Weifang; Hillsley, Kirk; **Davis, John B.**; Hicks, Gareth; **Winchester, Wendy J.**; Grundy, David
CORPORATE SOURCE:	Department of Biomedical Science, University of Sheffield, Sheffield, S10 2TN, UK
SOURCE:	Journal of Physiology (Oxford, United Kingdom) (2004), 560(3), 867-881 CODEN: JPHYA7; ISSN: 0022-3751
PUBLISHER:	Blackwell Publishing Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

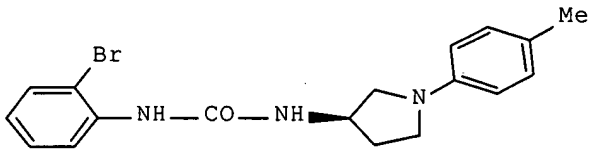
AB The aim of this study was to investigate the contribution of the TRPV1 receptor to jejunal afferent sensitivity in the murine intestine. Multiunit activity was recorded in vitro from mesenteric afferents supplying segments of mouse jejunum taken from wild-type (WT) and TRPV1 knockout (TRPV1-/-) animals. In WT prepns., ramp distension of the gut (up to 60 mmHg) produced biphasic changes in afferent activity so the pressure-response curve had an initial rapid increase in afferent discharge followed by a second phase of slower increase in activity. Afferent response to distension was significantly lower in TRPV1-/- than in WT mice. Single-unit anal. revealed three functional types of afferent fibers: (1) low-threshold fibers, (2) wide dynamic range fibers and (3) high-threshold fibers. There was a marked downward shift of the pressure-response curve for wide dynamic range fibers in the TRPV1-/- mice as compared to the WT controls. The afferent response to intraluminal hydrochloric acid (20 mM) was also attenuated in the TRPV1-/- mice. In contrast, the response to bath application of bradykinin (1 μM, 3 mL) was not significantly different between the two groups. The TRPV1 antagonist capsazepine (10 μM) significantly attenuated the nerve responses to distension, intraluminal acid and bradykinin, as well as the spontaneous discharge in WT mice. The WT jejunal afferents responded to capsaicin with rapid increases in afferent activity, whereas TRPV1-/- afferents were not at

all sensitive to capsaicin. Previous evidence indicates that TRPV1 is not mechanosensitive, so the results of the present study suggest that activation of TRPV1 may sensitize small intestinal afferent neurons.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

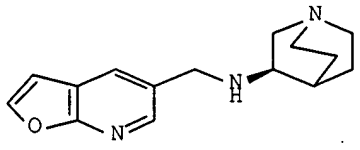
L16 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2003:253337 HCAPLUS Full-text
DOCUMENT NUMBER: 139:95331
TITLE: Neurogenic responses mediated by **vanilloid** receptor-1 (TRPV1) are blocked by the high affinity antagonist, iodo-resiniferatoxin
AUTHOR(S): Rigoni, Michela; Trevisani, Marcello; Gazzieri, David; Nadaletto, Riccardo; Tognetto, Michele; Creminon, Christophe; **Davis, John B.**; Campi, Barbara; Amadesi, Silvia; Geppetti, Pierangelo; Harrison, Selena
CORPORATE SOURCE: Department of Experimental & Clinical Medicine, Pharmacology Unit, University of Ferrara, Ferrara, 44100, Italy
SOURCE: British Journal of Pharmacology (2003), 138(5), 977-985
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Stimulation of the **vanilloid** receptor-1 (TRPV1) results in the activation of nociceptive and neurogenic inflammatory responses. Poor specificity and potency of TRPV1 antagonists has, however, limited the clarification of the physiol. role of TRPV1. Recently, iodo-resiniferatoxin (I-RTX) has been reported to bind as a high affinity antagonist at the native and heterologously expressed rat TRPV1. Here we have studied the ability of I-RTX to block a series of TRPV1 mediated nociceptive and neurogenic inflammatory responses in different species (including transfected human TRPV1). We have demonstrated that I-RTX inhibited capsaicin-induced mobilization of intracellular Ca2+ in rat trigeminal neurons (IC50 0.87 nM) and in HEK293 cells transfected with the human TRPV1 (IC50 0.071 nM). Furthermore, I-RTX significantly inhibited both capsaicin-induced CGRP release from slices of rat dorsal spinal cord (IC50 0.27 nM) and contraction of isolated guinea-pig and rat urinary bladder (pKB of 10.68 and 9.63, resp.), while I-RTX failed to alter the response to high KCl or SP. Finally, in vivo I-RTX significantly inhibited acetic acid-induced writhing in mice (ED50 0.42 μmol kg-1) and plasma extravasation in mouse urinary bladder (ED50 0.41 μmol kg-1). In vitro and in vivo TRPV1 activated responses to I-RTX was .apprx.3 log units and .apprx.20 times more potent than capsazepine, resp. This high affinity antagonist, I-RTX, may be an important tool for future studies in **pain** and neurogenic inflammatory models.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:453918 HCAPLUS Full-text
DOCUMENT NUMBER: 145:76019
TITLE: Discovery of SB-705498: A potent, selective and orally bioavailable TRPV1 antagonist suitable for clinical development
AUTHOR(S): Rami, Harshad K.; Thompson, Mervyn; Stemp, Geoffrey; Fell, Steve; Jerman, Jeffrey C.; Stevens, Alexander J.; Smart, Darren; Sargent, Becky; Sanderson, Dominic; Randall, Andrew D.; Gunthorpe, Martin J.; **Davis,**

John B.
CORPORATE SOURCE: Neurology and GI CEDD, GlaxoSmithKline, Essex, CM19 5AW, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(12), 3287-3291
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

AB Small mol. **antagonists** of the **vanilloid receptor** TRPV1 (also known as VR1) are disclosed. Pyrrolidinyl ureas such as (I) and (II) (SB-705498) emerged as lead compds. following optimization of the previously described urea SB-452533. Pharmacol. studies using electrophysiol. and FLIPR-Ca2+-based assays showed that compds. such as I and II were potent antagonists vs. the multiple chemical and phys. modes of TRPV1 activation (namely capsaicin, acid and noxious heat). Furthermore, II possessed suitable lead compound properties to enable progression of this compound into in vivo studies and subsequently clin. development.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:550885 HCAPLUS Full-text
DOCUMENT NUMBER: 141:99723
TITLE: Combinations of a **vanilloid** antagonist and an NSAID for the treatment of **pain**
INVENTOR(S): Bountra, Charanjit; **Davis, John Beresford**; Rami, Harshad Kantilal; Thompson, Mervyn
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004056394 A1 20040708 WO 2003-EP14776 20031217
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AU 2003294941 A1 20040714 AU 2003-294941 20031217
EP 1572237 A1 20050914 EP 2003-785923 20031217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
JP 2006512345 T2 20060413 JP 2004-561422 20031217
US 2006093687 A1 20060504 US 2005-540100 20050620
PRIORITY APPLN. INFO.: GB 2002-29808 A 20021220
WO 2003-EP14776 W 20031217

AB A method of treating conditions associated with **pain** and alleviating the symptoms associated therewith comprises administering to a mammal, including man, a **vanilloid** VR-1 antagonist or a pharmaceutically acceptable derivative thereof and an NSAID or a pharmaceutically acceptable derivative thereof, wherein said VR-1 antagonist or said NSAID may optionally be administered as a sub-maximal amount For example, a VR-1 antagonist, N-(2-bromophenyl)-N'-[((R)-1-(5- trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea (I) (preparation given), at oral dose 1 mg/kg and rofecoxib at oral dose of 1.5 mg/kg reversed a FCA-induced mech. hypersensitivity in guinea pigs by 32.5% and 30.6%, resp. However, combination of I and rofecoxib reversed the mech. hypersensitivity by 51.8%.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 6 OF 12 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2005044202 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15670270
TITLE: Vagal selective effects of ruthenium red on the jejunal afferent fibre response to ischaemia in the rat.
AUTHOR: Bulmer D C E; Jiang W; Hicks G A; **Davis J B**; **Winchester W J**; Grundy D
CORPORATE SOURCE: Department of Biomedical Sciences, University of Sheffield, Sheffield, UK.
SOURCE: Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society, (2005 Feb) Vol. 17, No. 1, pp. 102-11.
Journal code: 9432572. ISSN: 1350-1925.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 27 Jan 2005
Last Updated on STN: 10 Mar 2005
Entered Medline: 9 Mar 2005

AB A variety of inflammatory mediators and local metabolites, have been implicated in the sensitivity of intestinal afferent fibres to brief periods of ischaemia and reperfusion. As yet, the contribution of the vanilloid transient receptor potential (TRPV)1 receptor to the response to intestinal ischaemia remains undetermined. In the present study, the effect of pretreatment with the competitive TRPV1 antagonist capsazepine and the non-

selective TRPV channel antagonist ruthenium red, on the mesenteric afferent fibre response to ischaemia was examined. In control animals there was a reproducible biphasic increase in whole nerve afferent fibre activity during two brief periods of ischaemia. Treatment with ruthenium red significantly attenuated the early phase increase in afferent fibre activity during ischaemia. However, capsazepine treatment did not significantly alter the afferent fibre response to either ischaemia or reperfusion. Further experiments in chronically vagotomized animals indicated that the early phase response to ischaemia was mediated via vagal afferent fibres. The mechanism via which ruthenium red selectively inhibited vagal afferent fibres during ischaemia is unknown, but it does not appear to involve blockade of the TRPV1 receptor.

L16 ANSWER 7 OF 12 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006371067 EMBASE Full-text
TITLE: N-Tetrahydroquinolinyl, N-quinolinyl and N-isoquinolinyl biaryl carboxamides as antagonists of TRPV1.
AUTHOR: Westaway S.M.; Chung Y.-K.; **Davis J.B.**; Holland V.; Jerman J.C.; Medhurst S.J.; Rami H.K.; Stemp G.; Stevens A.J.; Thompson M.; Winborn K.Y.; Wright J.
CORPORATE SOURCE: S.M. Westaway, Neurology and GI Center of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park Third Ave, Harlow, Essex CM19 5AW, United Kingdom. sue.m.westaway@gsk.com
SOURCE: Bioorganic and Medicinal Chemistry Letters, (1 Sep 2006) Vol. 16, No. 17, pp. 4533-4536. .
Refs: 25
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(06)00687-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Aug 2006
Last Updated on STN: 24 Aug 2006

AB Starting from the high throughput screening hit (3), novel N-tetrahydroquinolinyl, N-quinolinyl and N-isoquinolinyl carboxamides have been identified as potent antagonists of the ion channel TRPV1. The N-quinolinylnicotinamide (46) showed excellent potency at human, guinea pig and rat TRPV1, a favourable in vitro DMPK profile and activity in an in vivo model of inflammatory **pain**. .COPYRGT. 2006.

L16 ANSWER 8 OF 12 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003074348 EMBASE Full-text
TITLE: Activation of **vanilloid** receptor 1 by resiniferatoxin mobilizes calcium from inositol 1,4,5-trisphosphate-sensitive stores.
AUTHOR: Marshall I.C.B.; Owen D.E.; Cripps T.V.; **Davis J.B.**; McNulty S.; Smart D.
CORPORATE SOURCE: I.C.B. Marshall, Neurol. Ctr. Excellence Drug Discov., GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, United Kingdom. Ian_C_Marshall@gsk.com
SOURCE: British Journal of Pharmacology, (2003) Vol. 138, No. 1,

pp. 172-176. .
Refs: 18
ISSN: 0007-1188 CODEN: BJPCBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2003
Last Updated on STN: 6 Mar 2003

AB 1. Capsaicin and resiniferatoxin (RTX) stimulate Ca(2+) influx by activating **vanilloid** receptor 1 (VR1), a ligand-gated Ca(2+) channel on sensory neurones. We investigated whether VR1 activation could also trigger Ca(2+) mobilization from intracellular Ca(2+) stores. 2. Human VR1-transfected HEK293 cells (hVR1-HEK293) were loaded with Fluo-3 or a mixture of Fluo-4 and Fura Red and imaged on a fluorometric imaging plate reader (FLIPR) and confocal microscope respectively. 3. In Ca(2+)-free media, RTX caused a transient elevation in intracellular free Ca(2+) concentration in hVR1-HEK293 cells (pEC(50) 6.45±0.05) but not in wild type cells. Capsaicin (100 μM) did not cause Ca(2+) mobilization under these conditions. 4. RTX-mediated Ca(2+) mobilization was inhibited by the VR1 **receptor antagonist** capsazepine (pIC(50) 5.84±0.04), the Ca(2+) pump inhibitor thapsigargin (pIC(50) 7.77±0.04), the phospholipase C inhibitor U-73122 (pIC(50) 5.35±0.05) and by depletion of inositol 1,4,5-trisphosphate-sensitive Ca(2+) stores by pretreatment with the acetylcholine-receptor agonist carbachol (20 μM, 2 min). These data suggest that RTX causes Ca(2+) mobilization from inositol 1,4,5-trisphosphate-sensitive Ca(2+) stores in hVR1-HEK293 cells. 5. In the presence of extracellular Ca(2+), both capsaicin-mediated and RTX-mediated Ca(2+) rises were attenuated by U-73122 (10 μM, 30 min) and thapsigargin (1 μM, 30 min). We conclude that VR1 is able to couple to Ca(2+) mobilization by a Ca(2+) dependent mechanism, mediated by capsaicin and RTX, and a Ca(2+) independent mechanism mediated by RTX alone.

L16 ANSWER 9 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:78415 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600085156
TITLE: Effects of VR1 receptor antagonism on responses to intestinal distension in the rat.
AUTHOR(S): **Winchester, Wendy**; Booth, Charlotte; Gaskin, Pam; **Davis, John**; Rami, Harshad; Hicks, Gareth
SOURCE: Gastroenterology, (APR 2004) Vol. 126, No. 4, Suppl. 2, pp. A428-A429.
Meeting Info.: Digestive Disease Week/105th Annual Meeting of the American-Gastroenterological-Association. New Orleans, LA, USA. May 16 -20, 2004. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jan 2006
Last Updated on STN: 25 Jan 2006

AB Background/Aims: VR1 receptor immunoreactivity has been demonstrated on both DRG and within the ENS. Furthermore, VR1 immunoreactivity is increased in patients with rectal hypersensitivity. Our aim was to investigate tire possible role of the VR1 receptor in the transmission of nociceptive signals

from the rat GI tract. Methods: 1. Extracellular jejunal afferent nerve recordings were obtained from pentobarbitone- anaesthetized male Sprague Dawley rats (330-450g). The effect of a VR1 receptor antagonist (2R)4-(3-chloropyridin-2-yl)-2-methyl-N-(4- trifluoromethylphenyl) piperazine -1-carboxamide (0.3, 3 & 10 mg/kg i.v.) upon responses to capsaicin (0.1 & 1 mu g/kg i.a.), or distension, in both naive and vagotomised rats was investigated. Isobaric ramp (2 mmHg every 4 sees, up to 60mmHg) and phasic distensions (10-50 mmHg 25 seconds) were performed. Some animals underwent chronic sub-diaphragmatic vagotomy (n=5), 5-10 days prior to study. 2. Abdominal electromyography (EMG) responses to colorectal distension (20, 40, 60 mm Hg, 2 min, 13 minutes apart) were obtained in conscious, unsedated mate Sprague-Dawley rats (300-400 g), pretreated I hr p.o. with either vehicle (1% methylcellulose 2ml/kg) or VR1 antagonist (10mg/kg). Data are mean +/- S.E.M. and analyzed using the Student's t-test or two-way ANOVA with Bonfferoni corrections, Results: Capsaicin (0.1 mu g/kg & 1 mu g/kg, i.a.) evoked dose-dependent increases in mesenteric afferent nerve discharge of 52 +/- 7 and 100 +/- 9 spikes/s, respectively. The VR1 antagonist (10mg/kg, i.v.) completely blocked the afferent responses to capsaicin. The VR1 antagonist (0.3-10mg/kg, i.v.) dose-dependently inhibited the afferent responses to ramp and phasic distensions at pressures of 30-50mmHg (phasic, $P < 0.05$) and 30-55mmHg (ramp, $P < 0.05$). In vagotomised animals, this effect of the VR1 antagonist was still observed to a similar degree (significant inhibition of the response at 10, 30-50 mmHg phasic and 35-60 mmHg, ramp, $P < 0.05$). The VR1 antagonist also significantly attenuated the EMG response to colorectal distension at 40mmHg ($p < 0.05$, n=7) but no effect was observed at either the low (20mmHg) or high (60mmHg) distension pressures. Conclusions: VR1 receptor antagonism attenuates a component of the afferent signal Iron) the intestinal tract in the noxious distending pressure range, and in the conscious animal, part of the behavioural EMG response to noxious distension. The VR1 receptor appears to be involved in the transmission of noxious sensory signals from the GI tract.

L16 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:144196 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400144196
TITLE: Identification and characterisation of SB-366791, a potent and selective **vanilloid receptor** (VR1/TRPV1) **antagonist**.
AUTHOR(S): Gunthorpe, M. J. [Reprint Author]; Rami, H. K.; Jerman, J. C.; Smart, D.; Gill, C. H.; Soffin, E. M.; Hannan, S. Luis; Lappin, S. C.; Egerton, J.; Smith, G. D.; Worby, A.; Howett, L.; Owen, D.; Nasir, S.; Davies, C. H.; Thompson, M.; Wyman, P. A.; Randall, A. D.; **Davis**, **J. B.**
CORPORATE SOURCE: Neurology and GI-CEDD, GlaxoSmithKline, New Frontiers Science Park, Harlow, Essex, CM19 5AW, UK martin_j_gunthorpe@gsk.com
SOURCE: Neuropharmacology, (Janaury 2004) Vol. 46, No. 1, pp. 133-149. print.
CODEN: NEPHBW. ISSN: 0028-3908.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004

AB **Vanilloid** receptor-1 (TRPV1) is a non-selective cation channel, predominantly expressed by peripheral sensory neurones, which is known to play a key role in the detection of noxious painful stimuli, such as capsaicin, acid and heat. To date, a number of antagonists have been used to study the physiological role of TRPV1; however, antagonists such as capsazepine are somewhat

compromised by non-selective actions at other receptors and apparent modality-specific properties. SB-366791 is a novel, potent, and selective, cinnamide TRPV1 antagonist isolated via high-throughput screening of a large chemical library. In a FLIPR-based Ca2+-assay, SB-366791 produced a concentration-dependent inhibition of the response to capsaicin with an apparent pKb of 7.74+-0.08. Schild analysis indicated a competitive mechanism of action with a pA2 of 7.71. In electrophysiological experiments, SB-366791 was demonstrated to be an effective antagonist of hTRPV1 when activated by different modalities, such as capsaicin, acid or noxious heat (50degreeC). Unlike capsazepine, SB-366791 was also an effective antagonist vs. the acid-mediated activation of hTRPV1. With the aim of defining a useful tool compound, we also profiled SB-366791 in a wide range of selectivity assays. SB-366791 had a good selectivity profile exhibiting little or no effect in a panel of 47 binding assays (containing a wide range of G-protein-coupled receptors and ion channels) and a number of electrophysiological assays including hippocampal synaptic transmission and action potential firing of locus coeruleus or dorsal raphe neurones. Furthermore, unlike capsazepine, SB-366791 had no effect on either the hyperpolarisation- activated current (Ih) or Voltage-gated Ca2+-channels (VGCC) in cultured rodent sensory neurones. In summary, SB-366791 is a new TRPV1 antagonist with high potency and an improved selectivity profile with respect to other commonly used TRPV1 antagonists. SB-366791 may therefore prove to be a useful tool to further study the biology of TRPV1.

L16 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:34254 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400032342
TITLE: INTESTINAL AFFERENT SENSITIVITY TO ACID AND DISTENSION IN WILD TYPE AND VR1-/- KNOCKOUT MICE.
AUTHOR(S): Hillsley, Kirk [Reprint Author]; **Winchester, Wendy J.**; **Davis, John B.**; Hicks, Gareth A.; Grundy, David
CORPORATE SOURCE: Sheffield, UK
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. S1694. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jan 2004
Last Updated on STN: 7 Jan 2004

AB Background: The vanilloid receptor-1 (VR1) is expressed predominantly in sensory neurones. Its role in somatic pain and inflammatory hyperalgesia has been well established following the generation of VR1 knockout animals (Caterina et al. Science. 2000; 288: 306-13). However, the role of VR1 in sensory signal transduction in visceral afferents has not been investigated. Methods: Experiments were performed on VR1-/- mice (Davis et al. Nature. 2000; 405: 183-7) and wild-type littermates. Mesenteric afferents were recorded using suction electrodes in vitro from segments of jejunum. The intestinal segment was bathed in Krebs buffer at 34oC and perfused intraluminally with saline for ramp distensions (<60mmHg), or with HCl (1-50 mM) for luminal acidification. Data are mean +- SEM are were compared with Students' t-tests as appropriate. Results: Mesenteric afferents in wild type but not VR1 -/- mice were activated by capsaicin (10 muM, DELTA=37.4+-

4.2imp./s) rapidly followed by desensitisation. There was no significant difference between wild type and VR1 -/- mice in either spontaneous discharge (9.1+-2.2imp/s vs 8.3+-1.7 respectively, p=0.78), or the response to ramp distension (DELTA at 60mmHg = 47.1+-8.7imp/s vs 48.3+-7.9 respectively, p=0.92). In both wild-type and VR1-/- mice, there was a biphasic response to ramp distension, with a rapid increase between 4-10 mmHg (1.7+-0.3imp/mmHg vs 2.0+-0.5imp/mmHg respectively, p=0.67), followed by a slower linear increase between 10-60 mmHg (0.8+-0.2imp/mmHg vs 0.7+-0.1imp/mmHg respectively, p=0.87). Following capsaicin desensitization in wild type mice, the afferent response to ramp distension was significantly attenuated both at low (0.8+-0.3imp/mmHg, p<0.05) and high (0.3+-0.2imp/mmHg, p<0.05) stimulus intensities. Intraluminal acid (gtoreq10 mM) evoked a similar increase in both wild type and VR1 -/- mice (10mM HCl =252.3+-41.9imp/120s vs 219.6+-54.2imp/120s respectively; 50mM =892.1+-130.6 imp/120s vs 865.9+-57.4 imp/120s respectively, p=0.84). However, following capsaicin desensitization the response to 50 mM HCl was significantly attenuated in wild type (77% reduction, p<0.01) but not VR1 -/- mice. Conclusions: These results demonstrate that both low and high threshold mechanoreceptors express the VR1 receptor, but these receptors are not directly involved in mechanotransduction. Similarly, the sensitivity of mesenteric afferents to luminal acid was independent of VR1 suggesting that in these transgenic animals there are other mechanisms that detect protons..

L16 ANSWER 12 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:25699 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400024098
TITLE: MOTOR ACTIVITY IN THE ISOLATED JEJUNUM OF VR1 KNOCKOUT MICE
.
AUTHOR(S): Rahmati, Reza [Reprint Author]; Cockerham, Michelle; Brunsden, Alan; Hillsley, Kirk; **Winchester, Wendy J.**; **Davis, John B.**; Hicks, Gareth A.; Grundy, David
CORPORATE SOURCE: Sheffield, UK
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. S1142. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Dec 2003
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AB Introduction: Isolated segments of mouse jejunum develop a complex pattern of contractile activity consisting of periods of phasic contractions that migrate in an aboral direction, interspersed by periods of quiescence (Abdu et al., Am. J. Physiol. 2002; 282:G624-33.). The aim of this study was to examine the role of vanilloid receptor-1 (VR1) in the generation of intestinal motor activity and its reflex modulation by intraluminal distension and acid. Methods: Experiments were performed on mice in which the VR1 gene had been disrupted using standard gene targeting techniques (Davis et al. Nature. 2000; 405: 183-7) and wild-type littermates. Jejunal contractile activity was recorded from in vitro segments of jejunum 4-5cm in length. When distended to 2-3 cm H2O the segments generated regular motor complexes (MCs) recorded as changes in intraluminal pressure. Data are mean +- SEM and analysed using

one-way ANOVA and pair-wise comparisons (Dunnett's method). Results: The periodicity and amplitude of MCs was similar in the knockout and wild-type jejunum (208.5+-18.6s and 7.5+-0.8cmH2O vs 201.6+-10.9s and 7.6+-0.6cmH2O respectively, n=10, NS). Capsaicin (1-100nM) caused a dose dependent inhibition of motility manifested as an increase in the interval between MCs in the wild-type animal only (e.g. 222+-39s to 393.8+-72s, at 100nM, N=5, P<0.05), a response abolished by pre-treatment with the VR-1 antagonist capsazepine (3mM). At higher doses of capsaicin (1-100muM), the periodic MCs were replaced by tonic increases in pressure upon which were superimposed phasic contractions at the slow wave frequency. This stimulation occurred in both knockout and wild-type mice and was unaffected by pre-treatment with capsazepine. Luminal acidification (10mM HCl) disrupted the generation of MCs which were replaced by continuous phasic activity superimposed upon small changes in tone that were not different between knockout and wild-type animals (1.5+-0.4cmH2O and 0.5+-0.3cmH2O) but significantly reduced from their corresponding control values (5.8+-0.5cmH2O and 6.0+-0.6cmH2O respectively, P<0.05, n=4). Conclusions: These data demonstrate that capsaicin acting on VR1 receptors, may exert an inhibitory influence on the enteric reflex circuits that control motor activity. Capsaicin also stimulates motility at higher doses via a non VR1 mediated mechanism, as seen in both knockout animal and after treatment with capsazepine. However, VR1 does not contribute to ongoing motor activity triggered by distension or the inhibitory effect of luminal acid..